IL-17A in COVID-19: a meta-analysis

Sukayna Fadlallah
American University of Beirut
Marcel Shams Eddin
American University of Beirut
Elias Rahal (er00@aub.edu.lb)
American University of Beirut

Article

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Abstract

IL-17A is a proinflammatory cytokine attributed with homeostatic roles but that is also involved in autoimmune disease pathogenesis. While some studies have reported an increase in IL-17A in subjects affected by COVID-19, no significant associations were found by others. Hence, we undertook this meta-analysis to examine whether serum IL-17A increases in COVID-19 patients. We report here that IL-17A increases in COVID-19 subjects irrespective of disease severity. It is also higher in patients with moderate disease compared to controls as well as higher in patients with severe COVID-19. While the increase in serum levels in subjects with severe disease over those with moderate disease was statistically significant, the association was not as robust as the other comparisons. Hence, IL-17A may be of relevance when considering management approaches to COVID-19; however, therapeutic approaches that target IL-17A should consider whether alleviation of inflammation outweighs eliminating the possible anti-viral roles of this cytokine.

Introduction

Coronavirus disease 2019 (COVID-19) is a notorious respiratory illness designated as a pandemic by the World Health Organization. The underlying infectious agent is the *Severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2), an emergent strain of the *Severe acute respiratory syndrome-related coronavirus* (SARSr-CoV) [1]. The novel disease was first reported in December 2019 in Wuhan, China but has since become an indisputable global burden. The contagion is mostly spread via respiratory droplets, upon close contact with an infected individual and from contaminated objects or surfaces. The incubation period is 2-14 days [2].The most common symptoms at onset are fever and dry cough with myalgia, fatigue and shortness of breath also possibly occurring. The viral pneumonia may become more severe with 6.1% of laboratory-confirmed cases progressing to a critical stage requiring mechanical ventilation, presenting with septic shock or requiring intensive care due to organ dysfunction or failure [3]. The estimated case fatality ratio is 1.38-3.67% with the mortality rate being highest in those older than 60 [4].

Infection with SARS-CoV-2 has been reported to result in increased levels of C-reactive protein, IL-1β, IL1-RA, IL-7, IL-2, IL-6, IL-8, IL-9, IL-10, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1A, MIP1B, PDGF, TNFα, and VEGF. Comparisons between severely affected individuals and those who were non-severe cases showed higher leukocyte and neutrophil counts but lower lymphocyte levels along with higher IL-2,IL-6, IL-7, IL-8, IL-10, GSCF, IP10, MCP1, MIP1A, and TNFα levels in the severe cases indicating a cytokine storm resulting in hyperinflammation [5, 6]. A decrease in B cells, T cells and NK cells was observed in all affected individuals but levels were more depressed in severe cases; functional assays however showed that this aspect was not affected by the infection. Analysis of particular T cell subsets showed a decrease in T helper cells, cytotoxic T cells and regulatory T cells [5]. Analysis of transcriptional changes in bronchoalveolar lavage fluid and peripheral blood mononuclear cells from SARS-CoV-2 patients not only demonstrated increased expression of inflammatory markers such as CCL2/MCP-1, CXCL10/IP-10, CCL3/MIP-1A, and CCL4/MIP1B, it also showed enhanced expression of p53 signaling and apoptosis markers, which may explain the lymphopenia observed with this infection [7].

An early case report indicated elevated levels of Th17 cells in the peripheral blood of SARS-CoV-2 infected patients [8]; Th17 cells produce IL-17A, a mediator associated with autoimmune processes and a cytokine that can induce the production of other proinflammatory mediators such as IL-1, IL-6, TNFα in addition to matrix metalloproteinases that may play a pertinent role in tissue damage [9]. The decrease in lymphocytic population subsets but rise in Th17 cells as well as increased levels of cytokines that fulfill the Th17 profile in these patients highly suggested that such an immune response drives the severe inflammation seen in these patients. Moreover, the mucins and fibrin-enriched edema seen in these patients is also suggestive of a possible role for IL-22, a Th17 cytokine that enhances the expression of fibrinogen and mucins [10]. These findings promopted the publication of several reviews, opinion pieces and commentaries advocating targeting of the Th17 pathway for therapeutic purposes or the utility of IL-17A as a possible marker of disease severity [10, 11, 12, 13, 14, 15, 16]. On the other hand, some reports indicated that T cells from COVID-19 patients do not markedly secrete IL-17A in response to antigens from the virus [17] and that Th17-related genes are downregulated in severe cases [18]. Moreover, a recent preprint by Meckiff, B.J. et al. [19] indicated that

Th17 cell subsets are underpresented amongst CD4+ T cells reactive to SARS-CoV-2 from COVID-19 patients compared to influenza-reactive CD4+ T cells from control subjects. Hence, we conducted a systematic review and meta-analysis to examine involvement of this pathway in COVID-19. With IL-17A being the effector molecule and more easily assessable marker of this pathway in laboratory evaluations, we examined reported IL-17A levels in sera from patients with different severity levels of COVID-19.

Results

A total of 7526 records were identified for review (Figure 1). Upon removal of duplicates, 3526 records were screened; of these, 22 papers described one or more COVID-19 patient subsets and an immune response pertaining to Th17. Twelve of the 22 papers satisfied all the inclusion criteria and reported serum levels of IL-17A in a COVID-19 patient subset and a control group or in at least two patient subsets. Hence, 12 studies were subsequently assessed (Table 1).

IL-17A in COVID-19 patients compared to controls

To assess IL-17A levels in controls and COVID-19 patients irrespective of the extent of disease severity, 8 studies were examined. These studies reported serum IL-17A in a control group as well as in subjects with COVID-19. For studies stratifying patient IL-17A levels based on disease severity, the weighted average levels and standard deviations were calculated to combine the patient groups per paper [30]. The studies by Lee, P.H. et al. and Xu, Z.S. et al. did not report a measure of variability for their control groups and hence a weighted standard deviation was imputed for their control group IL-17A levels utilizing those reported by the other studies included in this analysis by calculating the weighted standard deviation. IL-17A levels were hence assessed in 99 controls and 334 COVID-19 patients. Significantly higher levels of IL-17A were detected in COVID-19 patients compared to control subjects with a weighted mean difference (WMD) of 2.51 pg/ml (95% CI: 1.73-3.28, p<0.00001). The heterogeneity statistics τ^2 and I^2 were both 0% (Figure 2A). Since no heterogeneity was detected with the random effects model, a fixed effects model was also tested but that did not alter the outcome. A funnel plot was generated to assess publication bias (Figure 2B); conducting Egger's regression test and a rank correlation test for funnel plot asymmetry yielded p-values of 0.532 and 0.905, respectively, indicating no publication bias. Excluding studies with an imputed standard deviation did not alter the overall outcome [WMD=3.18 pg/ml (95% CI:1.83-4.53), p<0.00001, τ^2=0.53 and I^2=14%) (Supplementary Figure 1).

IL-17A in COVID-19 patients with moderate disease compared to controls

Five studies reported IL-17A levels in moderate COVID-19 subjects in addition to a control group. Hence, levels of this cytokine were assessed in 51 controls and 78 patients with moderate disease (Figure 3A). Using a random effects model, significantly higher levels of IL-17A were detected in the population of patients with moderate COVID-19 compared to controls [WMD= 2.41 pg/ml (95% CI:1.40-3.43), p<0.00001, τ^2=0 and I^2=0%]. A fixed effects model was also tested but that did not alter the overall outcome. A funnel plot was generated for assessing publication bias but none was detected with an Egger's test p=0.146 and a rank correlation test p=0.483 (Figure 3B). Since the standard deviations were imputed for the control group of the Xu, Z.S. et al. paper as described above, analysis was conducted excluding this paper; this did not affect the overall outcome as the effect of excluding the Xu, Z.S. et al. data from the analysis was negligible (Supplementary Figure 2) and IL-17A levels remained significantly higher in the moderate COVID-19 patient group compared to controls [WMD=2.42 pg/ml (95% CI:1.39-3.44), p<0.00001, τ^2=0 and I^2=0%].

IL-17A in COVID-19 patients with severe disease compared to controls

Six studies reported serum IL-17A levels in severely affected COVID-19 patients and in controls. Levels were therefore assessed in 61 controls and 69 severely-affected patients (Figure 4A). IL-17A was significantly higher in sera from patients with severe disease compared to control subjects [WMD=4.13 pg/ml (95% CI:1.65-6.60), p=0.001, τ^2=4.61 and I^2=55%]. A funnel plot was generated with an Egger's test and a rank correlation test p-values of 0.268 and 0.719, respectively, generally indicating no publication bias (Figure 4B). On the other hand, excluding the Xu, Z.S. et al. paper from the analysis, owing to the imputed

standard deviation employed for its control group IL-17A levels, did not alter the outcome and IL-17A serum levels remained significantly higher in the severe COVID-19 patient group compared to controls [WMD= 4.51 pg/ml (95% CI:1.71-7.32), p=0.002, τ^2=5.80 and I^2=64%] (Supplementary Figure 3). The Xu, Z.S. et al. paper had also included a group of 6 subjects with fatal COVID-19; inclusion of these subjects with the severe group and computing a weighted mean and standard deviation for the severe/fatal group also did not affect the overall outcome [WMD=4.01 pg/ml (95% CI:1.61-6.40), p=0.001, τ^2=4.41 and I^2=56%] (Figure 4C).

IL-17A in COVID-19 patients with severe disease compared to those with moderate disease

To assess if IL-17A serum levels may serve as a marker of COVID-19 severity, they were analyzed in 219 patients with moderate disease and 128 patients with severe disease; these levels were extracted from 9 studies (Figure 5A). A significant increase was observed in the severe group compared to the moderate group [WMD= 2.07 pg/ml (95% CI:0.20-3.95), p=0.03, τ^2=4.79 and I^2=91%]. A funnel plot was generated and asymmetry analysis was conducted obtaining an Egger's test p=0.650 and a rank correlation test p=1 indicating no publication bias (Figure 5B). Including the group of 6 subjects reported to have fatal COVID-19 in the Xu, Z.S. et al. paper in addition to the severe group did not affect the outcome [WMD=2.07 pg/ml (95% CI:0.20-3.94), p=0.03, τ^2=4.78 and I^2=91%] (Figure 5C).

Discussion

The hallmark of the Th17 response is the production of IL-17A, a cytokine with both homeostatic and pathologic effects. IL-17A is capable of activating a myriad of inflammatory pathways that may result in tissue damage and exacerbation of the disease. Several indicators had pointed at the possible involvement of IL-17A in COVID-19 clinical outcomes prompting suggestions of targeting this cytokine for therapeutic purposes or its use as a marker of disease severity [10, 11, 12, 13, 14, 15, 16]. Therefore, we undertook this systematic review and meta-analysis to examine the literature on this pathway with particular focus on IL-17A serum levels in COVID-19 patients. Our investigations indicate that IL-17A is significantly elevated in both moderate and severe cases of the disease compared to controls. Investigating the relationship between elevated levels of this cytokine and disease severity indicated that IL-17A levels are somewhat higher in the severe group than the moderate group; the WMD of serum IL-17A levels between moderate and severe subjects indicated a WMD of 2.07 pg/ml but a p-value of 0.03 and a lower 95% CI limit approaching zero; hence, while statistically significant, the relationship is not as strong as with other comparisons conducted in this meta-analysis; sensitivity analysis conducted by excluding each paper in this particular comparison at a time led to a loss of significance when excluding either of the Cacciapuoti, S. et al., Huang, C. et al., Liu, Y. et al., Ouyang, Y. et al., or Zhang, H. et al. papers. Hence, the association between serum IL-17A levels and disease severity is not robust. Arguably, inclusion of a larger cohort may enhance this significance; however, elevation of IL-17A is likely not a reliable and consistent marker of disease severity. An earlier meta-analysis that had examined IL-17A levels in moderate and severe cases of COVID-19 had also shown no elevated levels of IL-17A in the severe group over the moderate group; however, this meta-analysis had only included 3 papers assessing IL-17A levels [31].

The elevation of IL-17A in various COVID-19 groups may seemingly support targeting this cytokine in COVID-19 patients. Targeting IL-17A may be a useful approach since this cytokine promotes production of both IL-1 and IL-6 as well as neutrophil recruitment, several factors known to play a role in acute respiratory distress syndrome (ARDS) in COVID-19 [13]. Worth noting is that ixekizumab, the IL-17A inhibitor, is currently being investigated in combination with antiviral agents as an acute phase therapeutic option for the disease [32]. Although, IL-17A has been shown to enhance the expression of angiotensin-converting enzyme II (ACE2), the SARS-CoV-2 host cell entry receptor, in a human lung epithelial cell line [33], these effects may not necessarily take place *in vivo* or may not be sufficient to result in prolonged infection or severe disease. Notably, COVID-19 subjects with prolonged SARS-CoV-2 RNA shedding were reported to have lower levels of IL-17A during the acute phase of disease [24]; this may indicate that the net outcome of IL-17A elevation facilitates viral eradication despite its possible enhancement of viral entry receptor expression. This elevation may be a double-edged sword owing to its pro-inflammatory and tissue damaging effects. Moreover, IL-17A is believed to have homeostatic functions and its deficiency has been demonstrated to have detrimental effects in a cytokine release syndrome (CRS) mouse model [34]. Therefore, any consideration of agents that

may inhibit IL-17A or pathways related to this cytokine should include evaluation of the extent of inflammation and the possible anti-viral properties that may be inhibited by such a treatment.

This meta-analysis focused on a readily accessible marker for evaluation in patients, the serum level of IL-17A. With SARS-CoV-2 being a novel agent, the literature on this cytokine within the context of this infection remains lacking and few papers have examined this marker. Hence, this meta-analysis allowed for pooling the small population sizes assessed this far and hence permitted highlighting the elevation of serum IL-17A in COVID-19. On the other hand, the limitations of this study include that the majority of papers analyzed are from China, which may have been reflected in the low heterogeneity detected in some of our analyses. Underprivileged countries are also not represented in studies examining this marker; given that populaces in poorer countries have different sets of possible exposures, their immune responses may not necessarily be the same. Moreover, SARS-CoV-2 genomic variability, which in some instances appears to affect the virulence of this agent [35], and is likely related to the geographical location of the analyzed studies, is another possible confounder that remains unexamined. The age of the studied population is another factor that was difficult to control for; older individuals are prone to more severe complications with COVID-19 and the immune responses of older individuals naturally differ from younger subjects who predominate the control and moderate COVID-19 groups. The gender and race of the included subjects are other factors that may affect immune responses but that were not accounted for, mostly since attempting data stratification by these factors would result in loss of statistical power and also since this information was not available for most studies. Whether some of the individuals included in the study have an autoimmune disease or other conditions that could have resulted in increased IL-17A levels is also another unknown. Worth noting as well is that different types of assays were used in these different studies and that, although all samples tested were collected in the acute phase of disease, the time at which samples from the included subjects were obtained vary among the studies.

In conclusion, IL-17A is higher in subjects with COVID-19; how this increase affects the severity of infection should be further examined. Hence, any therapeutic approaches to this disease that target IL-17A should consider the benefit of possibly alleviating the inflammation and if this outweighs eliminating conceivable anti-viral roles that this cytokine may play.

Methods

Search strategy

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [36]. Four databases: Pubmed, Embase, Web of Science and CINAHL, were searched for papers published from January 1, 2019 to September 10, 2020. The literature was searched using the keywords T helper 17, Th17, Interleukin 17, IL-17, IL17, Interleukin 17A, IL-17A, IL17A, immune response, T cell response, inflammation or inflammatory response, and severe acute respiratory syndrome coronavirus 2, SARS-CoV2, SARS-COV-2, novel coronavirus, coronavirus disease 2019, COVID-19 or COVID19. A MeSH terms-based search strategy that did not account for the various iterations of the keywords referred to herein had resulted in omission of some pertinent papers. The bibliography of review and meta-analysis papers yielded by this search was also examined for referenced papers of interest.

Selection criteria

Paper titles, abstracts, full-texts, figures, tables and supplementary materials were examined by three independent reviewers (SF, MS, ER) and inclusion of papers was agreed to by the indicated reviewers. We included full-text papers reporting serum IL-17A levels in at least two COVID-19 patient severity types, or in one severity type and one control group in the meta-analysis. Papers reporting data duplicated elsewhere were excluded and hence the dataset was included only once. Papers only reporting high or low levels of serum IL-17A were not included in the meta-analysis nor were ones reporting Th17 cell percentages. Studies reporting IL-17A levels from COVID-19 patient cells in culture were excluded from the meta-analysis and so were ones reporting transcription-related expression levels or ones reporting serum IL-17A levels using a semi-quantitative assay. No language restriction was placed on paper inclusion. Preprints were not excluded.

Data extraction and quality assessment

Data was extracted from paper tables, figures and supplementary materials. IL-17A mean levels and standard deviations were either directly extracted, derived from paper figures, or computed from levels and measures of variability indicated, and then presented in pg/ml. Median and range or quartile data was used to derive means and standard deviations as per Luo, D. et al. [37] and Wan, X. et al. [38]. Individual subject levels reported as below detection limit were considered to be zero. Studies with missing data and those that required clarification were contacted by e-mail. Extracted data quality was assessed against the selection criteria and examined by the three independent reviewers. Due to the heterogeneity in patient severity nomenclature reporting, patient classification based on the World Health Organization COVID-19 case definitions was adopted [39]. For the purpose of this meta-analysis, mild and moderate patient groups were consolidated and labeled henceforth as “moderate”; severe and critical patient groups were also consolidated and labeled henceforth as “severe”.

Statistical analysis

Review Manager v5.4 (Cochrane Collaboration, Oxford, United Kingdom) was used for weighted mean difference and 95% confidence interval calculations as well as testing for the overall effect and for heterogeneity analysis. A random effects model was employed for all analyses; a fixed effects model was only used where specified in the results section for datasets with very low heterogeneity. For publication bias analysis, JASP v0.13.1 (JASP Team, Amsterdam, The Netherlands) was used to generate funnel plots and to conduct Egger’s regression and rank correlation tests for funnel plot asymmetry.

Data availability

Data supporting the findings of this study are included in the published manuscript and in the Supplementary information file or available from the corresponding author upon request.

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Declarations

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Contributions

ER conceptualized the work and contributed to data curation, analysis, writing and editing.

SF and MS contributed to data curation, analysis, writing and editing.

Authors SF and MS contributed equally to this work.

Competing interests

The authors declare no competing interests.

Tables

Table 1. Characteristics of papers included in the meta-analysis.

Study, Year (Ref.)	Country	Controls (n)	Moderate COVID-19 (n)	Severe COVID-19 (n)	Moderate/Severe COVID-19 (n)	Fatal COVID-19 (n)	Time of blood sampling	Study type
Cacciapuoti, S., 2020 [20]	Italy		7	28			At admission	Cross-sectional
De Biasi, S., 2020 [21]	Italy	15	23				Not specified	Cross-sectional
Fraser, D.D., 2020 [22]	Canada	10		10			At admission	Cross-sectional
Hadjadj, J., 2020 [23]	France	11	11	22			8-12 days after symptoms onset, before treatment	Cross-sectional
Huang, C., 2020 [6]	China	4	24	12			<4 days after admission	Cross-sectional
Lee, P.H., 2020 [24]	Singapore	23			158		Acute phase (median 8 days post-illness onset	Cross-sectional
Liu, Y., 2020 [25]	China	8	4	8			Multiple samples collected 0-15 days post-admission	Cross-sectional
Ouyang, Y., 2020 [18]	China		3	6			At admission	Cross-sectional
Song, J.W., 2020 [26]	China	24	29	10			Within 24 hrs of admission	Cross-sectional
Wan, S., 2020 [27]	China		102	21			After admission, prior to treatment	Cross-sectional
Xu, Z.S., 2020 [28]	China	4	10	7		6	Within 24 hrs of diagnosis	Cross-sectional
Zhang, H., 2020 [29]	China		29	14			On admission	Cross-sectional

Figures

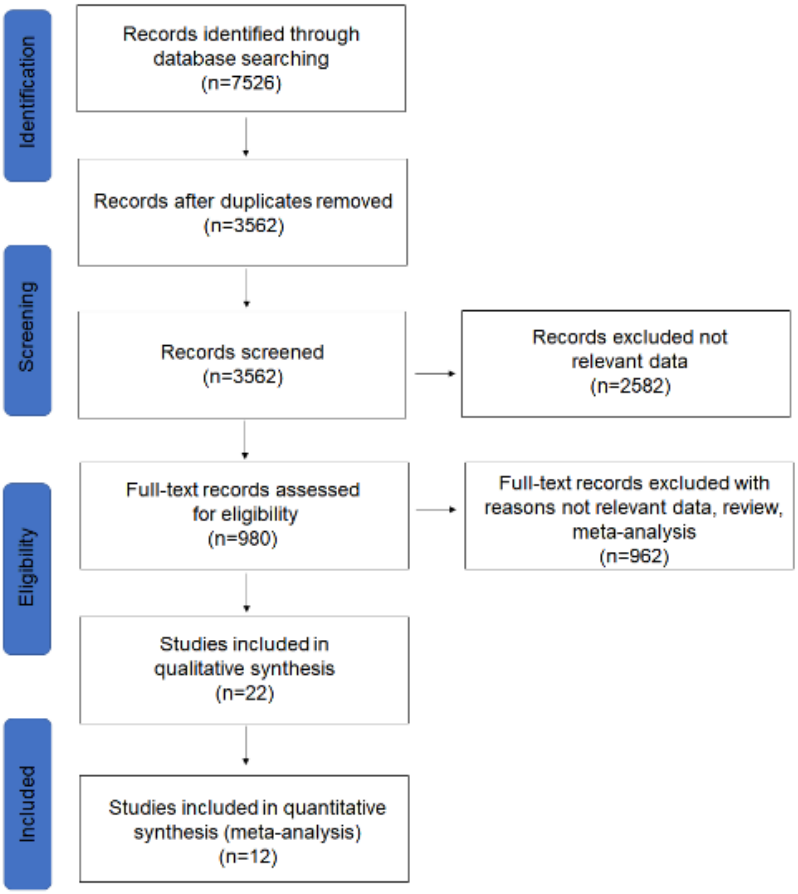
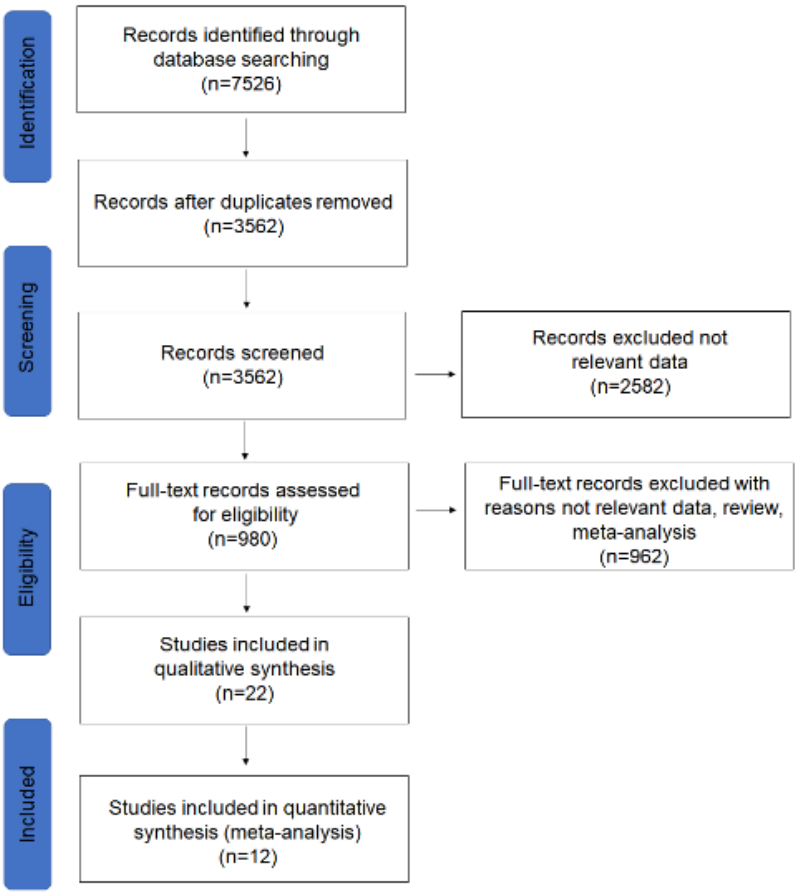


Figure 1

Serum IL-17A in COVID-19 systematic review and meta-analysis flow chart. Record screening and study inclusion was conducted as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.



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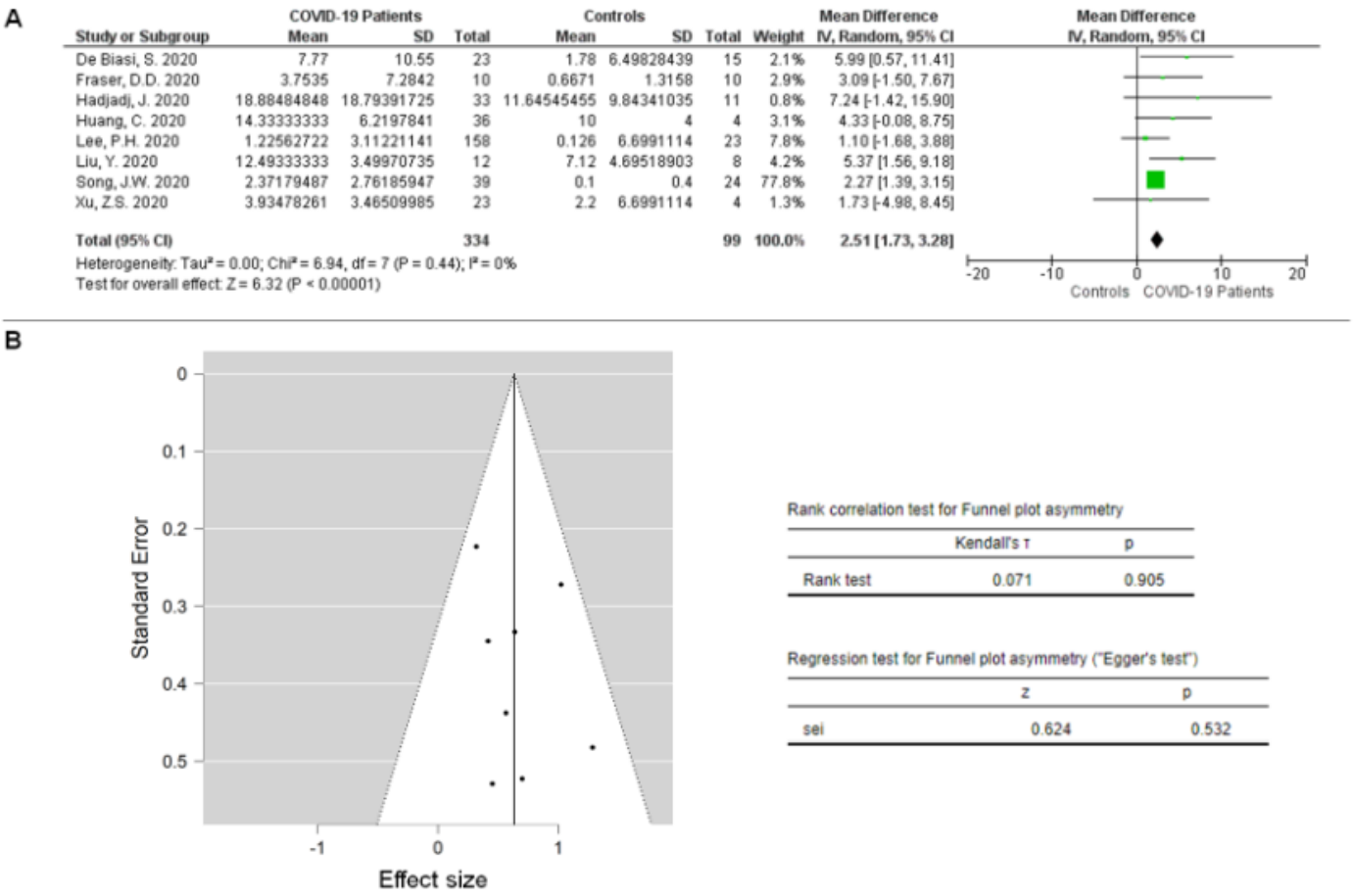
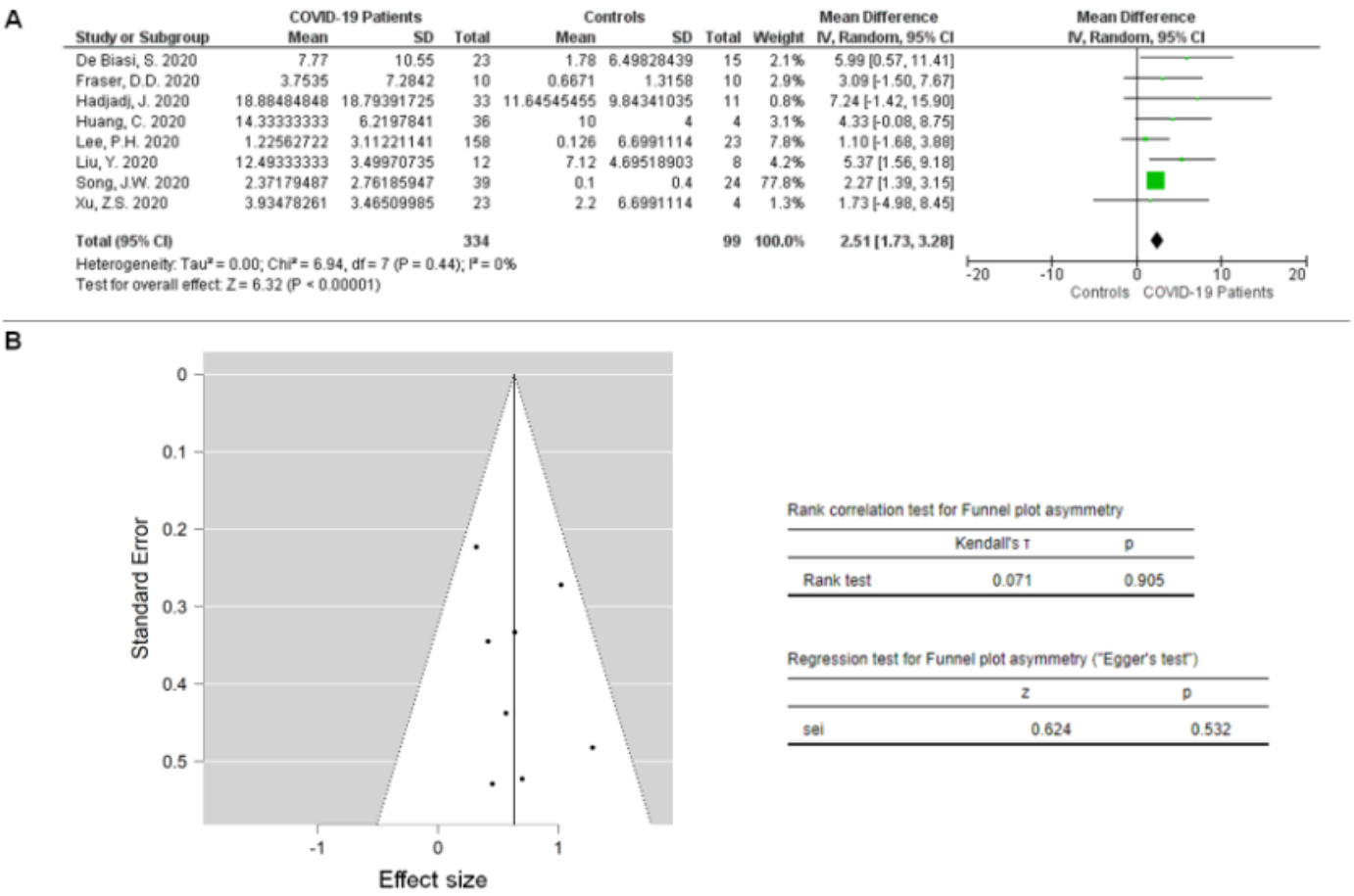


Figure 2

Serum IL-17A in COVID-19 patients compared to controls. (A) Forrest plot. (B) Funnel plot, Egger's regression and rank correlation tests.



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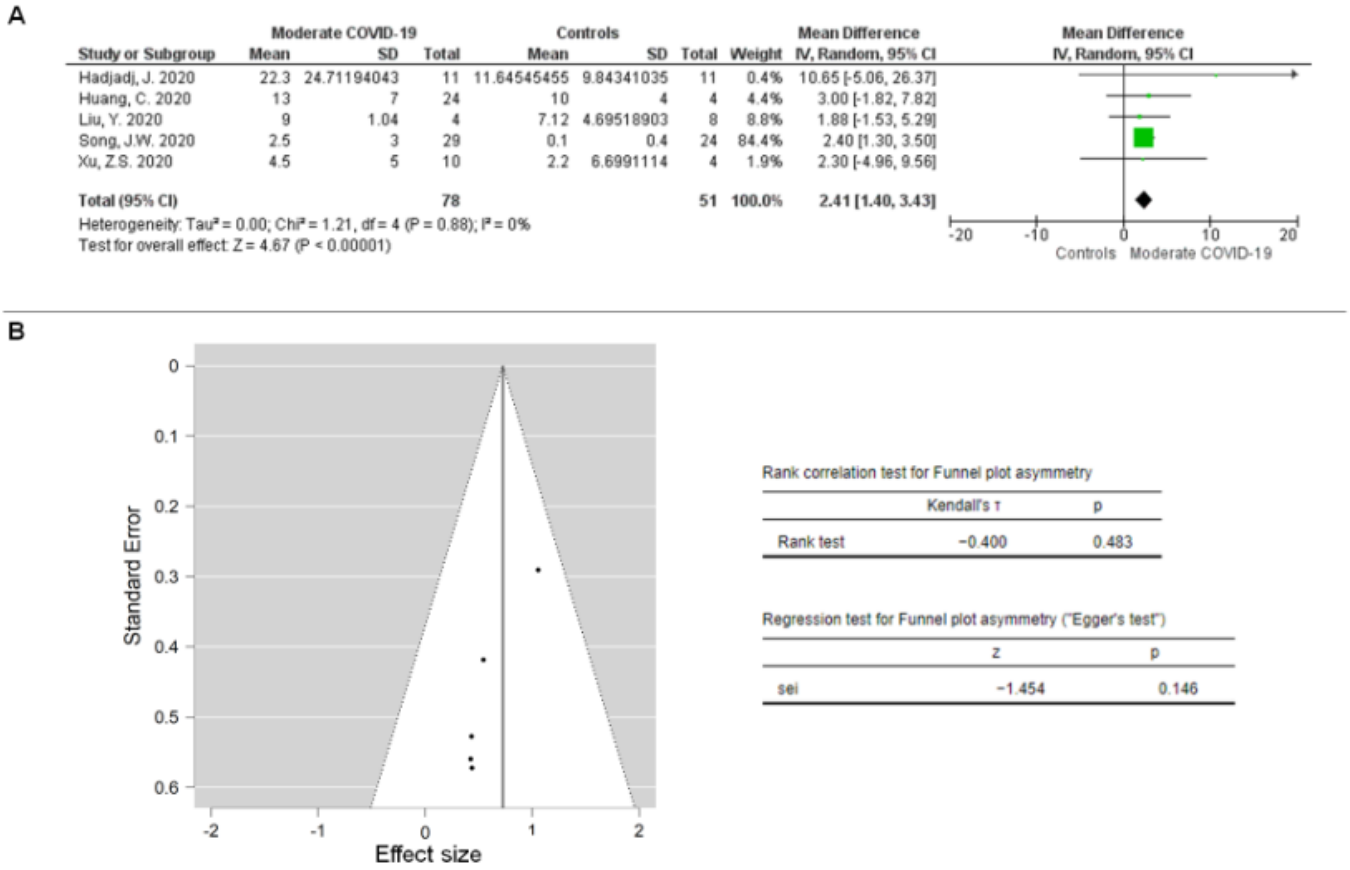
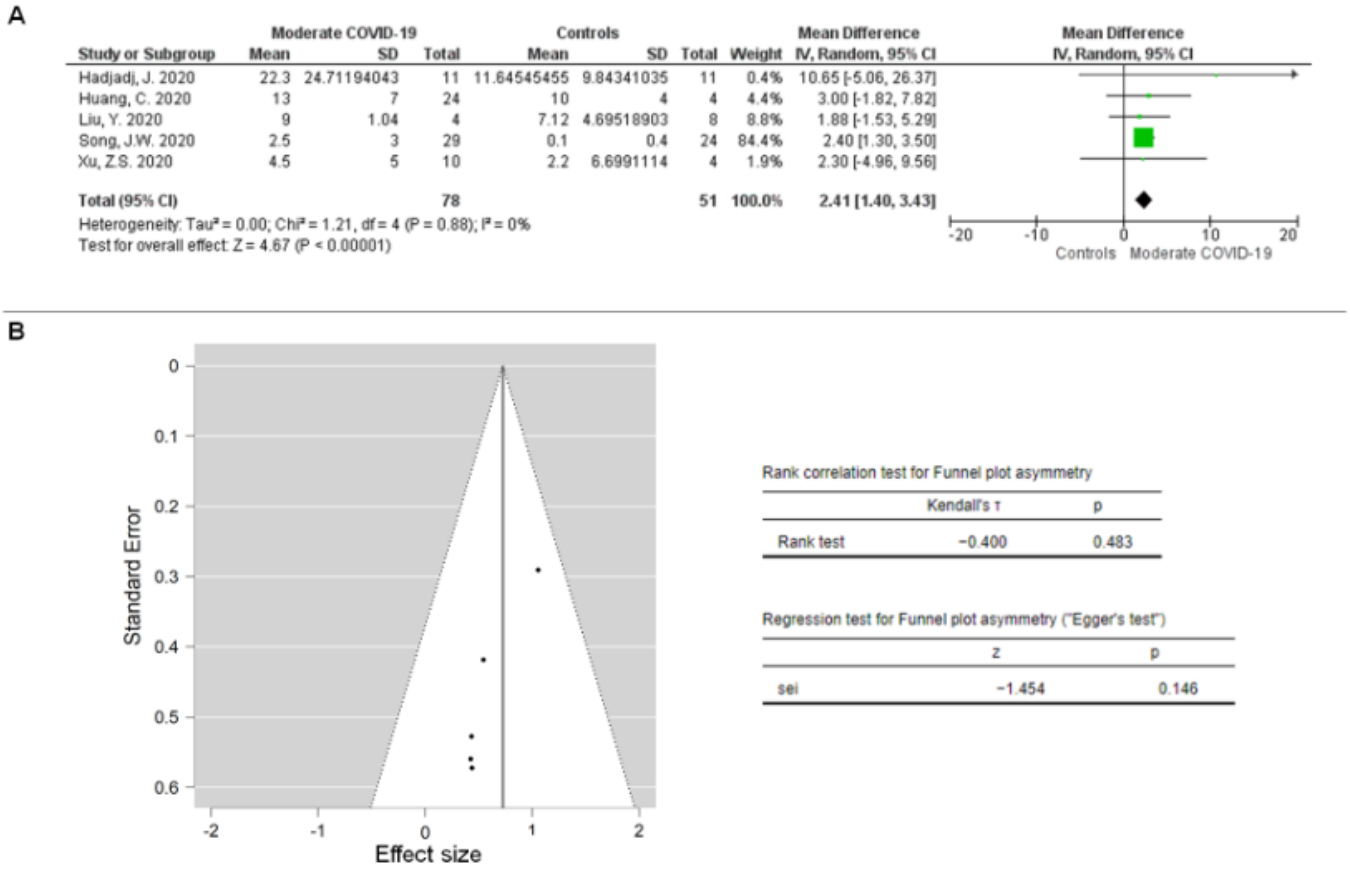


Figure 3

Serum IL-17A in COVID-19 patients with moderate disease compared to controls. (A) Forrest plot. (B) Funnel plot, Egger's regression and rank correlation tests.



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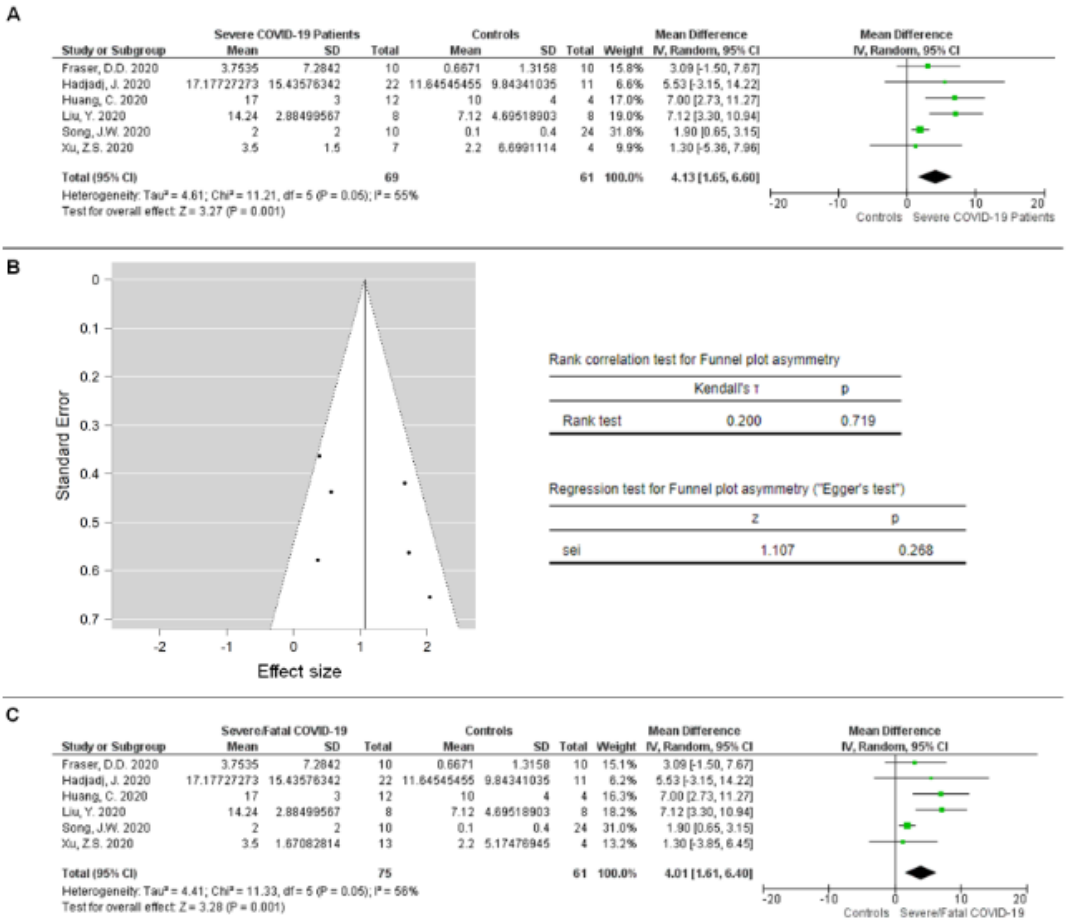

Figure 4

Serum IL-17A in COVID-19 patients with severe disease compared to controls. (A) Forrest plot. (B) Funnel plot, Egger's regression and rank correlation tests. (C) Forrest plot including subjects with fatal disease.

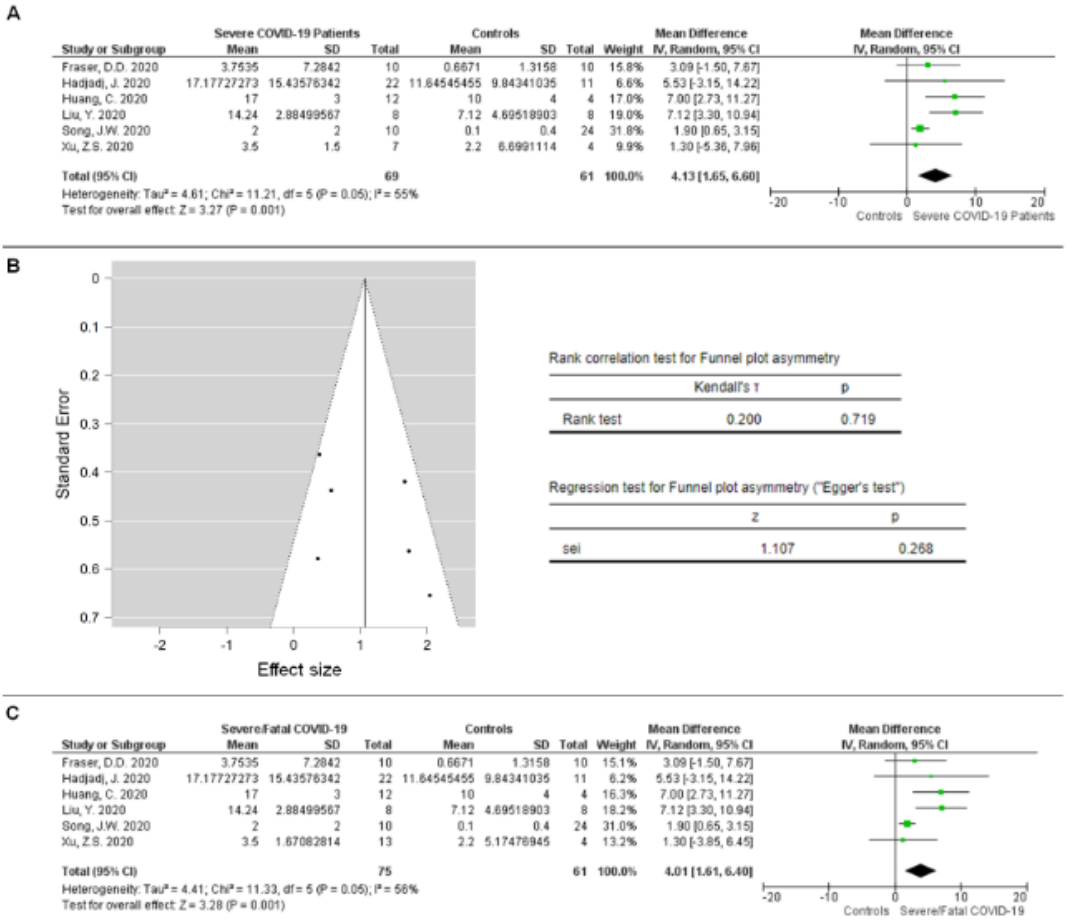

Figure 4

Serum IL-17A in COVID-19 patients with severe disease compared to controls. (A) Forrest plot. (B) Funnel plot, Egger's regression and rank correlation tests. (C) Forrest plot including subjects with fatal disease.

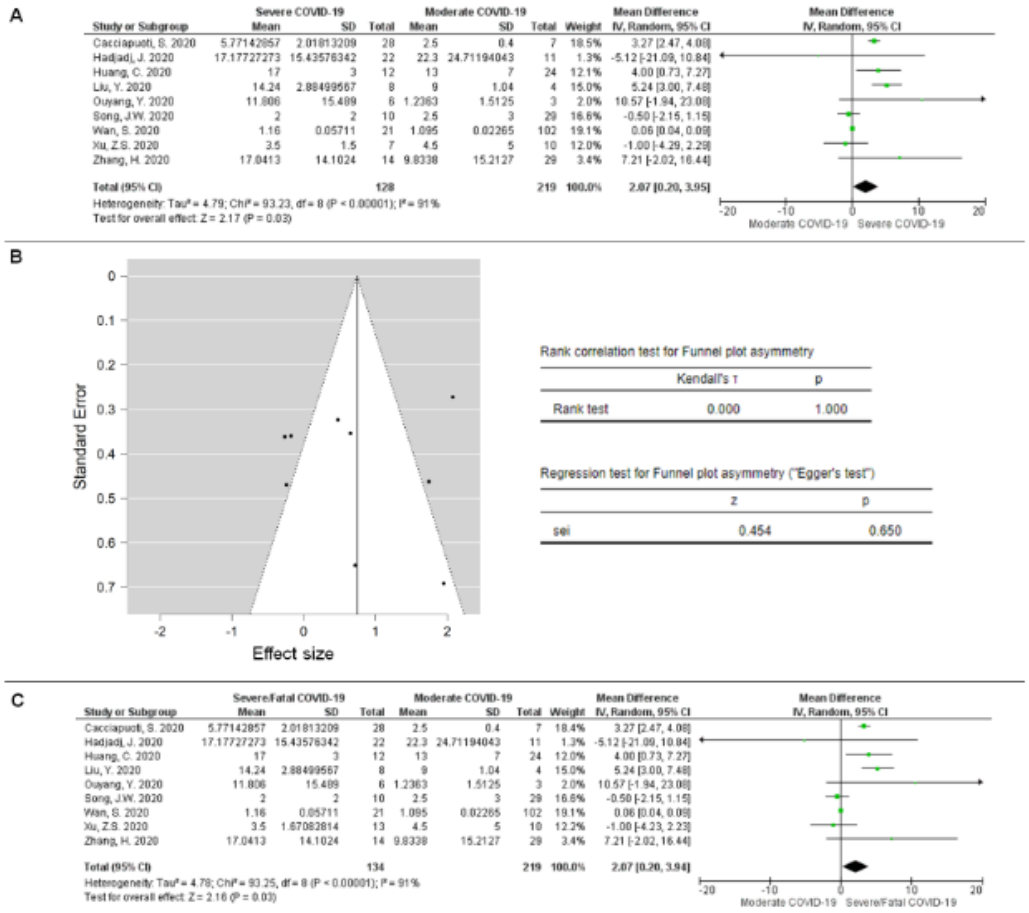

Figure 5

Serum IL-17A in COVID-19 patients with moderate disease compared to those with severe disease. (A) Forrest plot. (B) Funnel plot, Egger's regression and rank correlation tests.

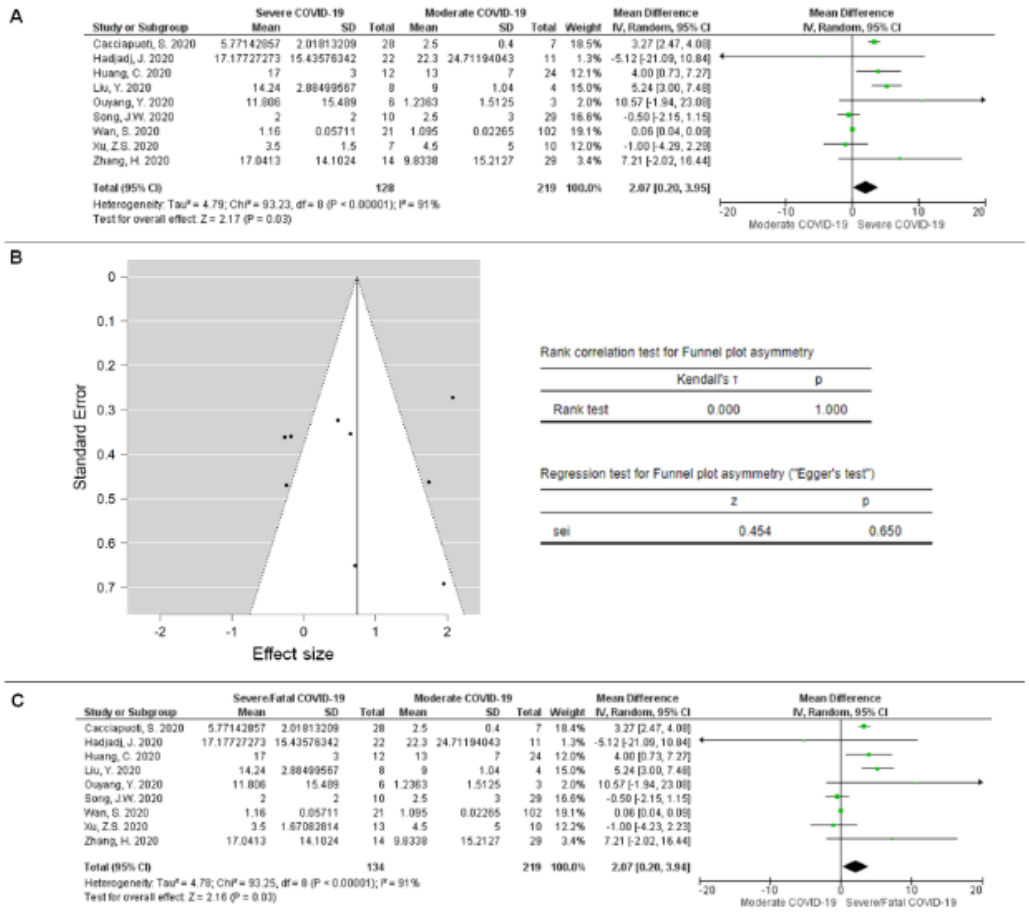

Figure 5

Serum IL-17A in COVID-19 patients with moderate disease compared to those with severe disease. (A) Forrest plot. (B) Funnel plot, Egger's regression and rank correlation tests.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementaryinformation.pdf
- Supplementaryinformation.pdf